Short Communication

Heterocyclic compounds bearing pyrimidine, oxazole and pyrazole moieties: design, computational, synthesis, characterization, antibacterial and molecular docking screening

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Keywords Pyrimidine · Oxazole · Pyrazole · Computational and antimicrobial

1 Introduction

The infections caused by the small pathogenic microbes could lead to the disease even a fetal one [1]. On the other hand spontaneous enhancement in the antimicrobial drug resistance to the available chemotherapeutic agents created so many problems in the treatment of infections caused by methicillin-resistant *Staphylococci aureus* (MRSA), penicillin resistant *Streptococcus pneumoniae* (PRSP) and vanco-mycin-resistant *Enterrococci* (VRE) [2]. Therefore, there is a continuous demand for the preparation of some new antibacterial agents for the treatment of these infections [3]. Heterocyclic compounds have been aimed a lot in the discovery of a variety of chemotherapeutic agents [4–8]. Piperonal moiety has been studied a lot due to its versatile biological applications like Antibacterial anti-cancer, anti-convulsant, anti-amoebic, anti-proliferative, antiviral, anti-tumor, anti-plasmodial, the COX-2 inhibitor [9–16]. Pyrimidine and its derivatives have been broadly studied by the researchers and reported to possess versatile biological potential such as antimicrobial, analgesic, antihistaminic, anti-bacterial, anti-protozoal, anti-tubercular, etc. [17–19]. The researchers targeted a lot on the therapeutic effects of pyrazole derivatives such as [20, 21]. On the other hand oxazole and its derivatives have been reported to possess numerous biological potential like anti-tubercular, antifungal, anti-HCV, agents, antimicrobial, antiproliferative, antitumor, anti-hyperglycemic or anti-diabetic, anticancer, antiviral, anti-inflammatory [22–31]. Recently El Shehryet al. [32] reported the synthesis and biological assessment of some quinoline derivatives containing pyrazole nucleus, another study aiming the antimicrobial therapeutic properties of the derivatives with nucleus (pyrazoles, isoxazoles, pyrimidine) were also reported by Padmaja et al. [33]. Some other studies targeting the biological potential and molecular docking assessment were also reported [34, 35]. The individual therapeutic effects of these nuclei (Piperonal, pyrazole, isoxazole, and Pyrimidine) prompted us to design and prepare some bioactive pyrimidine, pyrazole and oxazole derivatives bearing piperonal moiety and subjecting them for antimicrobial therapeutic potential as wells as molecular docking assessment.

2 Results and discussion

The structure of the target compounds (1–3) were drawn by the ChemDraw Ultra 8.0 software for the generation of the smiles. The smiles were then used for the calculation of bioactivity score and physicochemical analysis by Molinspiration, the calculated data is reported in Fig. 1. The bioactive compounds (1-3) were then synthesized by the schematic procedure mentioned in Fig. 2. The step-1, of the synthetic procedure included the condensation reaction in between the 1,3-benzodioxole-5-carbaldehyde

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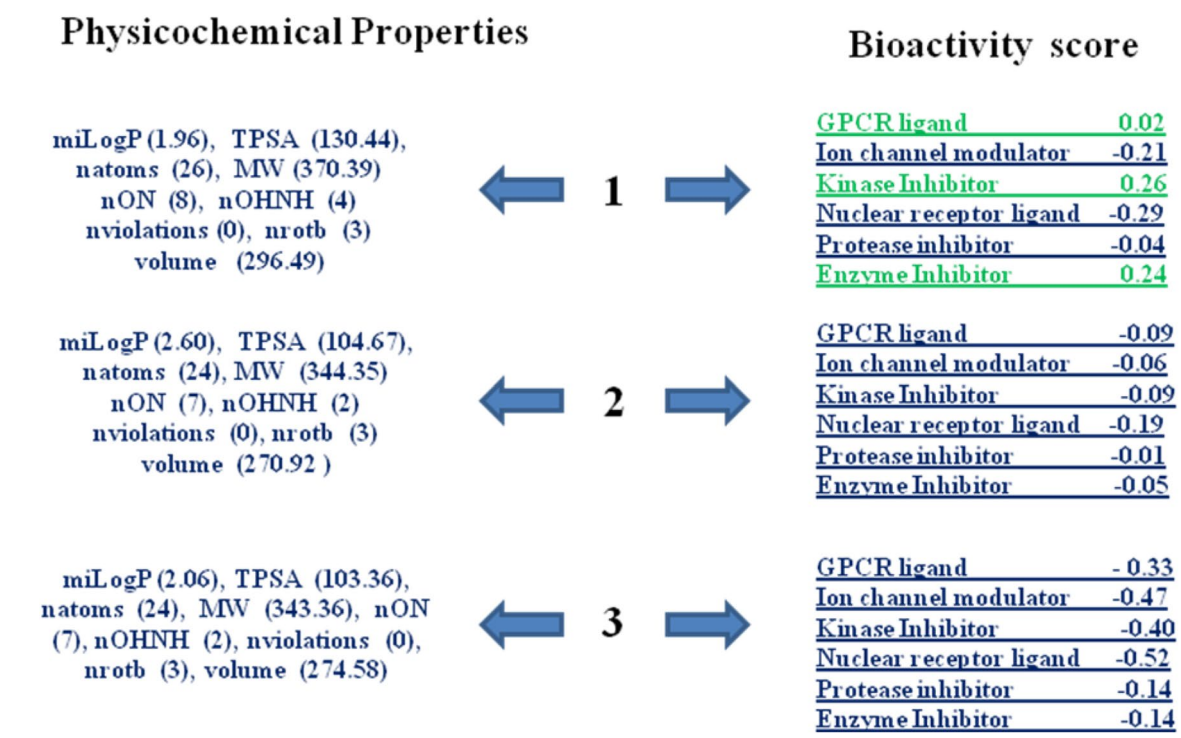
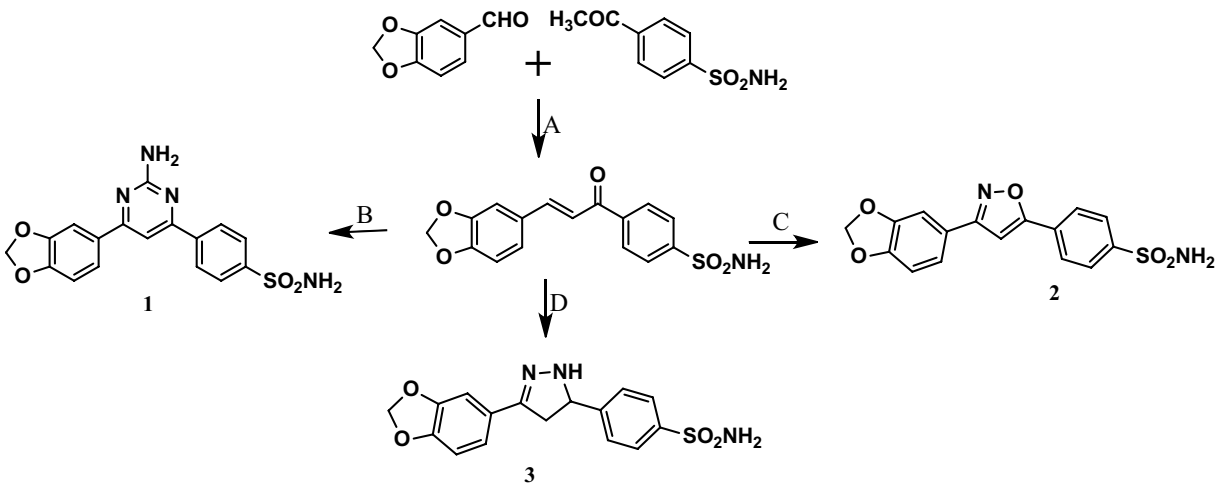


Fig. 1 Representing the drug likeness properties (physicochemical and bioactivity score) for the compounds (1–3)



A= NaOH, Ethanol, reflux, B= Guanidine hydrochloric acid, isopropyl alcohol, reflux
C= $NH_2OH.HCl$, Ethanol, reflux D= $NH_2NH_2.H_2O$, Conc. H_2SO_4, Ethanol, reflux

Fig. 2 Representing the schematic diagram for the synthesis of compounds (1–3)

and 4-acetylbenzenesulfonamide to yield of 4-[(2*E*)-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]benzenesulfonamide (A). The step-2 is different for the synthesis of compounds 4-[2-amino-6-(1,3-benzodioxol-5-yl) pyrimidin-4-yl]benzenesulfonamide [1], 4-[3-(1,3-benzodioxol-5-yl)-1,2-oxazol-5-yl]benzenesulfonamide [2] and -[5-(1,3-benzodioxol-5-yl)-4*H*-pyrazol-3-yl]benzenesulfonamide [3]. The compounds-1 undergoes the reaction (A) and guanidine hydrochloride in isopropanol under reflux condition. Compound-A reacted with hydroxylamine hydrochloride in ethanol under reflux, to yield compound-2. The compound-3 is synthesized through

the reaction between hydrazine hydrate and compound-A, in ethanol under reflux condition. The compounds (1–3), were then characterized for the structural confirmation by many spectroscopic methods (FT-IR, ^{1}H-NMR, Mass spectroscopy) and elemental analysis. The FTIR spectra for compound-1 exhibited the signal at 1063, 1617, 3335, 3354 cm^{-1} due to the presence of C–N, C=N, NH_2, SO_2–NH_2 functional groups and the absence of signal around 1700 cm^{-1} due to C=O functional group confirmed the structure of the compound-1. The disappearance of the signal around 1700 cm^{-1} due to the C=O functional group and the appearance of signals in the range 1619–1621, 2971–2977 and 3347–3358 cm^{-1} due to the presence of C=N, CH-Ar, SO_2–NH_2 functional groups confirmed the formation of compound-2 and compound-3. Further structural confirmation was carried out by the ^{1}H-NMR spectra for compounds (1), the characteristic singlet at 5.971 ppm due to O–CH_2–O protons, 8.114 ppm due to NH_2 protons and 8.393 ppm due to SO_2–NH_2 protons. The H-NMR spectra of the compounds 2–3 exhibited the singlet around 5.908–8.310 ppm and 8.310–8.408 due to the O–CH_2–O and SO_2–NH_2 protons respectively. The spectra of compound-3 also exhibited the double doublets around 3.19–3.26, 4.07–4.15 and 6.10–6.17 ppm due to the presence of H_A, H_B, H_X protons of the pyrazoline nucleus. The experimental section possessed the detailed spectroscopic data of the compounds (1–3). The screening of compounds as antimicrobial agents) was assessed by the method of disc diffusion, using the gram-positive and negative pathogens in as per the formation of inhibition zone and minimum inhibitory concentration (MIC). The respective zone of inhibition and MIC of the compounds (1–3) and reference drug Ciprofloxacin is represented in the Table 1 and the %Area of inhibition/µg is reported in Fig. 3. The results for antimicrobial screening portrayed that compound-1 possessed very strong similarity with the reference the drug, Compound-2 exhibited very significant antimicrobial effect against all microorganisms, while the compound-3 was found to possess better the antimicrobial effect in comparison to the reference drug.

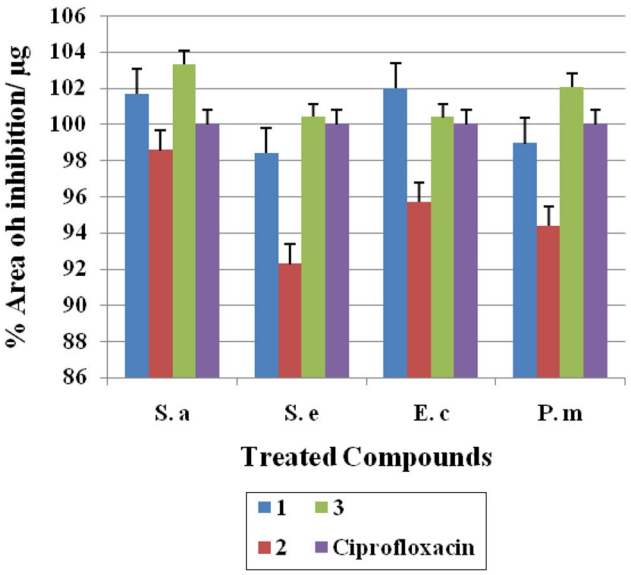


Fig. 3 Representing the percent area of inhibition per microgram of the treated compounds (1–3) and standard drug ciprofloxacin

To understand the cyto-toxicity status of the synthesized compounds the MTT assay was performed against HepG2 cells. The synthesized compounds were treated HepG2 cells with the different concentrations (3.125, 6.25. 12.5, 25, 50 and 100 µM) and observed that the viability of the cells were inversely proportional to the concentration (Fig. 4). According to the protocol only the viable cells will be able to produce the formazan crystal due to the presence of mitochondrial enzymes so the formation of the colored complex will be equal to the number of viable cells. To support the experimental results and for better understanding of the antimicrobial potential molecular docking assessment was performed for all the synthesized compounds (1–3) and the Ciprofloxacin. The results exhibited that a variety of the residues of GlcN-6-P-synthase were observed of forming the Hydrogen bond with the Compound-1 (SER 316, TYR 576, ASP 548), Compound-2 (LYS 487 and LEU 480), Compound-3 (CYS 300, SER 347, SER 401 VAL399, ILE

Table 1 Representing the zone of inhibition and the minimum inhibitory concentrations of the compounds (1–3) and ciprofloxacin

S. no.	Diameter of the halo zone, mm and minimum inhibitory concentration (MIC)							
	Gram-positive				Gram-negative			
	S. aureus		*S. epidermidis*		*E. coli*		*P. mirabilis*	
	Zone of inhibition	MIC	Zone of inhibition	MIC	Zone of inhibition	MIC	Zone of inhibition	MIC
1	21.75 ± 0.18	6.25	22.50 ± 0.20	3.125	24.16 ± 0.36	6.25	22.10 ± 0.32	12.5
2	21.08 ± 0.25	6.25	21.10 ± 0.36	3.125	22.67 ± 0.22	6.25	21.08 ± 0.25	12.5
3	22.10 ± 0.14	6.25	22.96 ± 0.26	3.125	23.78 ± 0.20	6.25	22.80 ± 0.23	12.5
Cipro	21.39 ± 0.21	6.25	22.87 ± 0.37	3.125	23.69 ± 0.81	6.25	22.34 ± 0.21	12.5

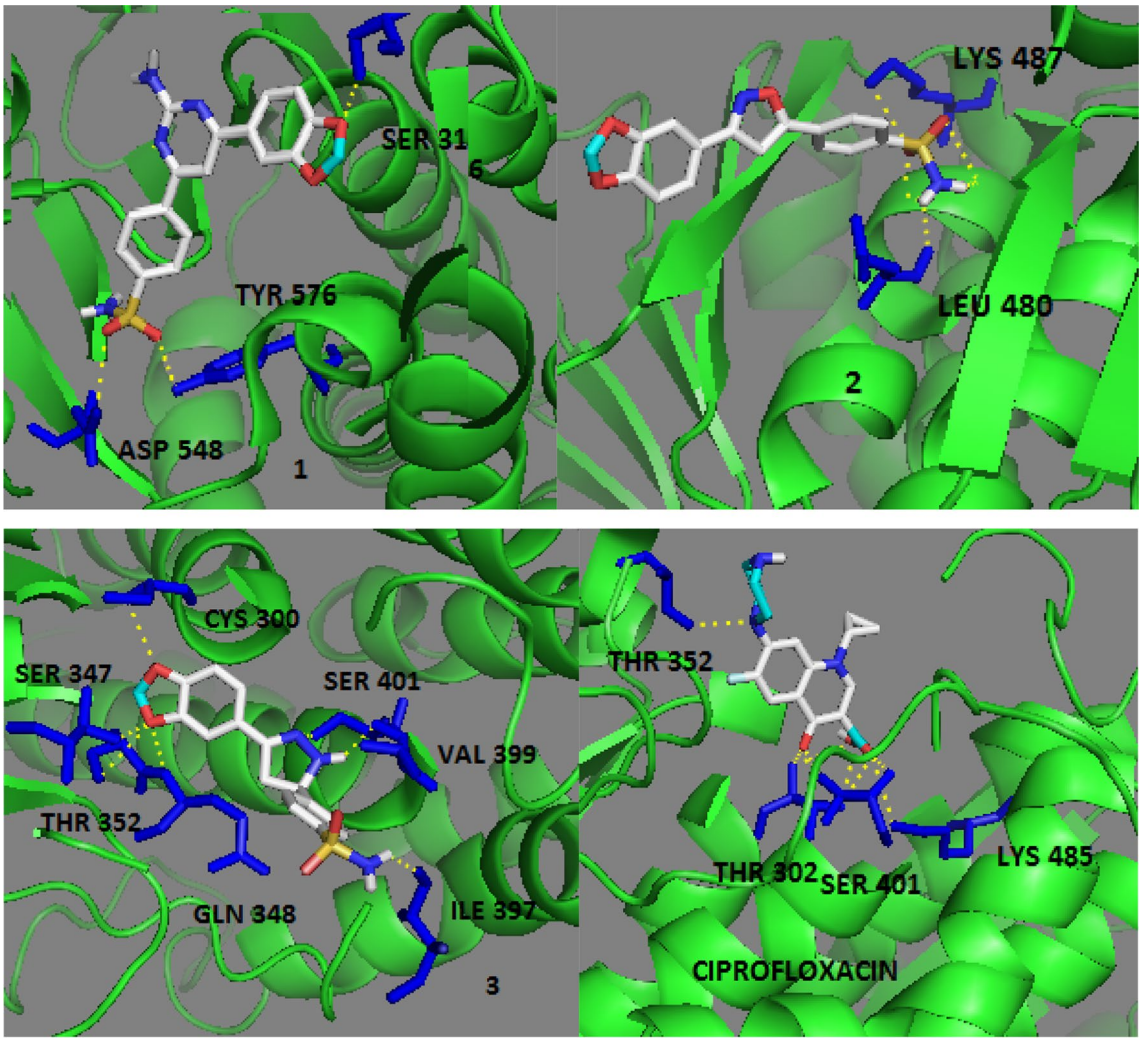


Fig. 4 Molecular docking images for the compounds (1–3) and ciprofloxacin

397, GLN 348 and THR 352) and Ciprofloxacin (THR 352, THR 302, SER 401 and LYS 485). Overall the docking assessment strongly recommended the experimental results and revealed that compound-3 represented too much better H-bonding than the Ciprofloxacin and the similar H-bonding is observed with only SER residues (Compound-1, 3 & Ciprofloxacin) and SER & THR residues (Compound-3 & Ciprofloxacin), Fig. 5. The binding affinity of the compound-1, 2, 3 and the ciprofloxacin was observed respectively in the range – 7.5 to – 7.0 kcal/mol, (– 7.0 to – 6.5 kcal/mol), (– 7.6 to – 6.6 kcal/mol) and (– 7.1 to 6.2 kcal/mol) Table 2.

3 Experimental

The schematic diagram and the structures of the compounds were drawn by ChemDraw Ultra 8.0 ChemSketch, and the computational study was performed on the Molinspiration. The required chemicals and reagents Piperonal, 4-acetylbenzenesulfonamide, NaOH, Ethanol, Guanidine hydrochloric acid, isopropyl alcohol, NH_2OH. HCl, reflux, NH_2NH_2.H2O, Conc. H_2SO_4, agar, ciprofloxacin, dimethylsulfoxide, MTT, DMEM, FBS) were purchased from Sigma-Aldrich, Merck, Germany, HIMEDIA and HyClone Laboratories, Logan, UT, USA. Estimation of the progress of the reaction was performed by the thin layer chromatographic plates. Analytical techniques to confirm the structure were performed by Heraeus Vario EL III analyzer for elemental analysis, Perkin-Elmer model 1600 FT-IR RX1 instrument for FTIR spectra, Spectra Bruker Avance 300 MHz spectrometer for NMR (^{1}H or ^{13}C) spectra and Micromass Quattro II triple quadrupole mass spectrometer for mass spectra.

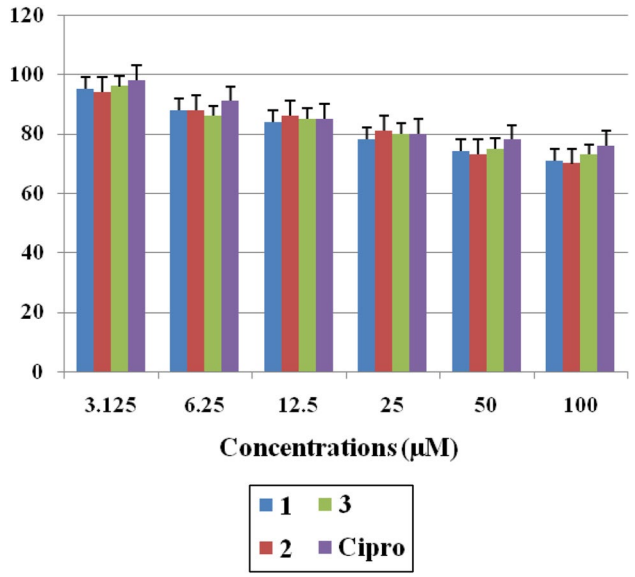


Fig. 5 Representing the percent viability of HepG2 cells on treatment of compounds (1–3) and standard drug ciprofloxacin

3.1 Computational assessment

Chem Draw ultra 8.0 was used to design the structures of the compounds (1–3), standard and applied for the calculation of physicochemical properties and bioactivity score by the online available software (Molinspiration), the detailed procedure is reported in [36–42].

3.2 Synthesis and characterization

3.2.1 General procedure for the synthesis of 4-[(2E)-3-(1,3-benzodioxol-5-yl)prop-2-enoyl] benzenesulfonamide

The synthesis of 4-[(2*E*)-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]benzenesulfonamide was performed by the procedure reported in [17].

3.2.2 Procedure for the synthesis of 4-[2-amino-6-(1,3-benzodioxol-5-yl)pyrimidin-4-yl] benzenesulfonamide [1]

4-[(2*E*)-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]benzenesulfonamide and guanidine hydrochloride was taken in the round bottom flask, mixed with 50 mL of isopropyl alcohol and refluxed for 24 h to yield the desired compound [1].

3.2.3 4-[2-amino-6-(1,3-benzodioxol-5-yl)pyrimidin-4-yl] benzenesulfonamide

Yield: 85%; m. p. 115–117 °C: Light Yellow crystals; Anal. calc. for $C_{17}H_{14}N_4O_4S$: C 55.13, H 3.81, N 15.13; Found: C 55.09, H 3.84, N 15.17; FT-IR (cm^{-1}): 1063 (C–N), 1617 (C=N), 2995 (CH-Ar), 3335 (NH_2), 3354 (SO_2–NH_2); ^{1}H NMR (DMSO-d6) (ppm): 5.971 (s, 2H, O–CH_2–O), 6.858 (s, 1H, CH-Ar), 7.039–7.121 (d, 1H, CH-Ar), 7.198–7.231 (d, 1H, CH-Ar), 7.337–7.502 (m, 4H, CH-Ar), 8.114 (s, 2H, NH_2), 8.393 (s, 2H, SO_2NH_2); ESI–MS (m/z): [M^+ + 1]: 371.08 (Mass: 370.39).

Table 2 Representing the binding affinities of all the nine modes of binding with the residues of receptor (GlcN-6-P-synthase), and the distance from the best mode (upper bound or lower bound)

Modes	Compound-1			Compound-2			Compound-3		
	Binding affinity (Kcal/mol)	Distance from best mode		Binding affinity (Kcal/mol)	Distance from best mode		Binding affinity (Kcal/mol)	Distance from best mode	
		rmsd l.b	rmsd u.b		rmsd l.b	rmsd u.b		rmsd l.b	rmsd u.b
1	−7.5	0.000	0.000	−7.0	0.000	0.000	−7.6	0.000	0.000
2	−7.3	28.732	30.334	−7.0	19.292	25.433	−7.4	12.245	14.816
3	−7.2	25.757	27.707	−6.7	9.359	13.519	−7.4	27.567	28.495
4	−7.1	4.144	5.934	−6.7	19.442	24.303	−7.4	22.066	23.674
5	−7.1	25.344	26.747	−6.7	31.710	33.237	−7.1	12.792	15.899
6	−7.1	26.760	28.847	−6.7	15.761	20.197	−7.1	2.218	2.490
7	−7.1	25.833	26.960	−6.6	17.402	18.548	−7.0	27.671	29.141
8	−7.0	19.117	20.386	−6.6	17.092	18.429	−6.6	22.633	24.277
9	−7.0	27.047	28.012	−6.5	8.792	11.936	−6.6	28.546	29.466

3.2.4 Procedure for the synthesis of 4-[3-(1,3-benzodioxol-5-yl)-1,2-oxazol-5-yl] benzenesulfonamide [2]

An equimolar amount of 4-[(2*E*)-3-(1,3-benzodioxol-5-yl) prop-2-enoyl]benzenesulfonamide and hydroxylamine hydrochloride were added to 50 mL ethanol and refluxed for 24 h. The resulting compound was obtained in the form of precipitate, filtered, dried under vacuum and recrystallized from methanol.

3.2.5 4-[3-(1,3-benzodioxol-5-yl)-1,2-oxazol-5-yl] benzenesulfonamide

Yield: 88%; m. p. 110–112 °C: Light Yellow crystals; Anal. calc. for $C_{16}H_{12}N_2O_5S$: C 55.81, H 3.51, N 8.14; Found: C 55.83, H 3.52, N 8.17; FT-IR (cm^{-1}): 1621 (C=N), 2977 (CH-Ar), 3347 (SO_2–NH_2); ^{1}H NMR (DMSO-d6) (ppm): 5.908 (s, 2H, O–CH_2–O), 6.905 (s, 1H, CH-Ar), 7.139-7.181 (d, 1H, CH-Ar), 7.283-7.320 (d, 1H, CH-Ar), 7.363-7.492 (m, 4H, CH-Ar), 8.310 (s, 2H, SO_2NH_2); ESI–MS (m/z): [M^+ + 1]: 345.05 (Mass: 344.35).

3.2.6 Procedure for the synthesis of 4-[5-(1,3-benzodioxol-5-yl)-4H-pyrazol-3-yl] benzenesulfonamide [3]

Hydrazine hydrate and 4-[(2*E*)-3-(1,3-benzodioxol-5-yl) prop-2-enoyl]benzenesulfonamide were mixed in 50 mL of ethanol in a round bottom flask and kept on refluxing and following the addition of sulfuric acid (1 mL). On completion of the reaction the reaction mixture was poured to the cold water to yield the final product.

3.2.7 4-[5-(1,3-benzodioxol-5-yl)-4H-pyrazol-3-yl] benzenesulfonamide [3]

Yield: 80%; m. p. 119–121 °C: Dark Yellow crystals; Anal. calc. for $C_{16}H_{13}N_3O_4S$: C 55.97, H 3.82, N 12.24; Found: C 55.99, H 3.84, N 12.26; FT-IR (cm^{-1}): 1619 (C=N), 2971 (CH-Ar), 3358 (SO_2–NH_2); 3.19-3.26 (dd, 1H, pyrazoline ring, H_B), 4.07–4.15 (dd, 1H, pyrazoline ring, H_A), 6.10–6.17 (dd, 1H, pyrazoline ring, H_X), ^{1}H NMR (DMSO-d6) (ppm): 6.007 (s, 2H, O–CH_2–O), 6.881 (s, 1H, CH-Ar), 7.039–7.095 (d, 1H, CH-Ar), 7.252–7.395 (m, 4H, CH-Ar), 8.402 (s, 2H, SO_2NH_2), 11.113 (s, 1H, NH); ESI–MS (m/z): [M^+ + 1]: 344.07 (Mass: 343.36).

3.3 Antimicrobial screening

Antimicrobial screening of the compounds (1–3) was performed by disc diffusion on the gram positive and gram-negative pathogens [*S. aureus* (ATCC-25923), *S. epidermidis* (ATCC-29887), *E. coli* (ATCC-25922), *P. mirabilis* (ATCC-25933) following the same protocol as discussed in the literature [43–53].

3.4 Molecular docking assessment

Molecular docking assessment was performed by Aautodock-tools 1.5.6, Autodock-Vina, and Pymol to estimate the binding affinity and the H-bonding in between the synthesized compounds (1–3), ciprofloxacin with the amino acid residues of the protein GlcN-6-P-synthase, (PDB: 2VF5) [54–56].

3.5 Percent viability of the cells assessment

The percent viability of the cells for the prepared compounds 1-3 was performed against HepG2 (Human hepatocellular carcinoma). The cells were grown Dulbecco's modified Eagle's medium with 10% heat-activated fetal bovine serum, and (100 units/mL penicillin, 100 mg/mL streptomycin and 2.5 mg/mL amphotericin B) and incubated at 37 °C in an atmosphere containing (95% air/5% CO_2), [57, 58].

4 Conclusion

A series of three compounds with different heterocyclic nucleus was designed and calculated for bioactivity and physicochemical properties. The compounds were found to possess the bioactivity score in the zone for bioactive compounds. The compounds were synthesized, characterized and evaluated for antimicrobial effects and the findings revealed that the compound-3 portrayed better antimicrobial potential than ciprofloxacin. Molecular docking assessment was also established for a better understanding of the antimicrobial potential in terms of binding affinity and H-bonding with the residues of GlcN-6-P-synthase. The Results of the docking assessment strongly recommended the experimental finding and represented that compound-3 has better H-bonding with the protein residues than the standard.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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